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Title: Temporal trends in survival following ward-based NIV for acute hypercapnic respiratory failure in patients with COPD.

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Abstract:

Introduction: Non-invasive ventilation (NIV) is recommended for treatment of acute hypercapnic respiratory failure (AHRF) ~~refractory to medical management~~ in ~~patients with~~ acute exacerbations of COPD. National UK audit data suggests that mortality rates are rising in COPD patients treated with NIV.

Objective: To investigate temporal trends in in-hospital mortality in COPD patients undergoing a first episode of ward-based NIV for AHRF.

Methods: Retrospective study of hospitalised COPD patients treated with a first episode of ward-based NIV at a large UK teaching hospital between 2004 to 2017. Patients were split into two cohorts based on year of admission, 2004-2010 (Cohort 1) and 2013-2017 (Cohort 2), to facilitate comparison of patient characteristics ~~and in-hospital mortality~~.

Results: In total, 547 unique patients were studied. There was no difference in in-hospital mortality rate between the time periods studied (17.6% vs. 20.5%, p=0.378). In Cohort 2 there were more females, a higher rate of co-morbid bronchiectasis and ~~a higher rate of~~ pneumonia on admission ~~, higher rate of co-morbid bronchiectasis~~and more severe acidosis, hypercapnia and hypoxia. ~~,~~ More patients in Cohort 2 had ~~greater proportion of patients with~~ NIV as the ceiling of treatment. Patients in Cohort 2 experienced a~~,~~ longer time from AHRF diagnosis to application of NIV, higher maximum inspiratory positive airway pressure, lower maximum oxygen and~~,~~ shorter duration of NIV. ~~,~~Finally, patients in Cohort 2 experienced a ~~-~~shorter hospital length of stay (LOS), with no differences observed in rate of transfer to critical care or intubation. ~~in hospital and more severe acidosis, hypercapnia and hypoxia.~~

Conclusion: In-hospital mortality remained stable and LOS decreased over time, despite greater comorbidity and more severe AHRF in COPD patients treated for the first time with ward-based NIV ~~for AHRF~~. ~~This study highlights a need for evaluation of factors influencing clinician decisions to manage patients with concomitant pneumonia and severe AHRF with ward-based NIV.~~

Key words: chronic obstructive pulmonary disease; acute exacerbation; acute hypercapnic respiratory failure; non-invasive ventilation; trends; survival; mortality.

Introduction:

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide [1]. A significant increase in the rate of acute exacerbations of COPD (AECOPD) has been observed in England with many patients requiring hospitalisation [2]. Acute hypercapnic respiratory failure (AHRF) occurs in around 20% of hospitalised patients with AECOPD and is associated with increased mortality [3,4]. Non-invasive ventilation (NIV) is recommended for the treatment of AHRF refractory to optimal medical management [5,6]. The survival benefits associated with NIV seen in 'real life' data have been smaller than the original randomised controlled trials and the literature describing long-term outcomes is limited [7,8]. This study aimed to investigate temporal trends in in-hospital mortality in COPD patients treated with ward-based NIV for AHRF.

Methods:

Hospitalised COPD patients undergoing a first episode of ward-based NIV for AHRF at a large teaching hospital in the West Midlands (UK) were prospectively enrolled into the NIV department registry between July 2004 to November 2017. Patients were selected for ward-based NIV as per Trust protocol (Figure 1) and NIV was delivered on an 11 bed, respiratory physiotherapist lead unit according to national guidelines. Nurses and physiotherapists underwent protocolised training to deliver ward-based NIV. The nurse-to-patient ratio was determined using an acuity-based nursing staffing level scoring system which calculates the number of nurses needed to staff the NIV unit safely (2-4 nurses). NIV was delivered continuously and patients were weaned as per Trust protocol. Pre-NIV arterial blood gas results were entered prospectively into the registry by NIV physiotherapists. Clinical diagnoses of COPD were confirmed with spirometry demonstrating an FEV_1/FVC ratio <0.7. In patients without spirometry, discharge letters, respiratory clinic letters, chest x-rays and computed tomography (CT) findings were also reviewed to verify clinical diagnoses. Admission chest x-ray reports were reviewed to confirm or refute diagnoses of pneumonia. CT scans were reviewed for evidence of bronchiectasis. Data were analysed in STATA version 15 (StataCorp, Texas, USA). The cohort was split into two groups based on year of admission, 2004-2010 and 2013-2017, to facilitate comparison of patient characteristics and in-hospital mortality. The years 2011-2012 were excluded due to incomplete data capture during this time.

Results:

In total, 547 unique patients were studied. Patient characteristics are summarised in Table 1. Overall, 104 patients (19%) died in-hospital during their first episode of ward-based NIV for AHRF. There was no statistically significant difference in rate of in-hospital mortality between Cohort 1 and Cohort 2. In the Cohort 2 there were more females, a higher rate of pneumonia on admission, higher rate of co-morbid bronchiectasis, higher FEV_1, greater proportion of patients with NIV as the ceiling of treatment, longer time from respiratory failure diagnosis to application of NIV, higher maximum IPAP, lower maximum oxygen, shorter duration of NIV, shorter length of stay in hospital and more severe acidosis, hypercapnia and hypoxia.

Discussion:

There was no evidence to support a difference in in-hospital mortality between the time periods studied. Our in-hospital mortality was higher than the original randomised controlled trials advocating the use of NIV in AECOPD however it was lower the in-hospital mortality rate of 25.1% reported by the recent National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) [7,8].

Despite the stability of in-hospital mortality over time, we found that patients in Cohort 2 had more severe acidosis, hypercapnia and hypoxia. In keeping with data from the NCEPOD report, our findings may reflect increased confidence and a willingness to manage patients with worse blood gas results on the ward, rather than transferring them to critical care, this requires further study [8,9]. Interestingly, despite guidelines recommending against the use of ward-based NIV in patients with pneumonia [5], we found that more patients in the Cohort 2 had concomitant pneumonia on admission chest x-ray. This may, in part, be due to a greater proportion of patients in Cohort 2 having NIV as their ceiling of treatment. However, this may also suggest that clinicians are choosing to utilise ward-based NIV more frequently in COPD patients with AHRF and pneumonia, rather than escalating to critical care. We cannot rule out the possibility that patients had been escalated to critical care and subsequently had been deemed unsuitable for transfer by the assessing clinicians. A prospective study is required which adequately captures data regarding if patients had been escalated to critical care and if ward-based NIV was placed as the ceiling of treatment.

We observed a slightly longer time difference between diagnosis of AHRF and application of NIV in the Cohort 2. The increasing frequency of emergency department attendances and emergency hospital admissions in England may result in slower intra-hospital transfer times and a longer time to initiate NIV. This study highlights a possible need for quality improvement to meet the recently published BTS 'Quality Standards for acute non-invasive ventilation in adults' statement: "Patients who meet evidence-based criteria for acute NIV should start NIV within 60min of the blood gas result associated with the clinical decision to provide NIV and within 120min of hospital arrival for patients who present acutely." [10]. The observation that there were fewer males in Cohort 2 was unexpected and may reflect an increasing prevalence of COPD in females in England [11].

Patients in Cohort 2 received a higher maximum IPAP and a lower maximum oxygen; this likely reflects greater understanding of acute NIV and the evidence-base for higher pressures and controlled oxygen therapy in AECOPD [5]. We observed a higher rate of bronchiectasis in Cohort 2 which we suspect may reflect an increase in diagnostic CT scanning, rather than increased incidence. Whilst we observed a higher FEV_1 % predicted in Cohort 2 (35% vs 32%) this is not considered a clinically important difference and both cohorts demonstrated severe airflow obstruction. Finally, we observed a shorter duration of NIV treatment and a shorter length of hospital stay in Cohort 2, of approximately 1 day and 2 days respectively. The evolution of community and integrated care in COPD along with increased demand for inpatient beds in the UK may explain the bed occupancy reduction, however the reasons for these findings are likely to be multifactorial and require further investigation. Increased confidence acquired over the past decade in the delivery of ward-based NIV in AECOPD may have contributed to the shorter duration of NIV treatment in patients in Cohort 2. Additionally, increased provision of domiciliary NIV for COPD patients with hypercapnic respiratory failure may facilitate faster weaning from acute NIV and discharge from hospital.

Key strengths of this study include the large cohort size, long observation period and reliability of COPD diagnoses. Limitations include the single centre, retrospective design and uncontrolled observational cohort nature of this study.

In summary, in-hospital mortality remained stable over time in COPD patients treated for the first time with ward-based NIV for AHRF. Patients in Cohort 2 had more severe AHRF, a higher rate of pneumonia and a shorter hospital stay. This study highlights a need for further evaluation of factors

influencing clinician decisions to manage patients with concomitant pneumonia and severe AHRF with ward-based NIV rather than managing them in critical care.

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Table 1: Participant characteristics for the whole cohort and for patients split based on year of hospital admission – Cohort 1 (2004-2010) and Cohort 2 (2013-2017).

	Median [IQR] or n (%)			
Characteristic	**Total (n=547)**	**Cohort 1 (n=279)**	**Cohort 2 (n=268)**	**P value**
Age (years)	70.6 [63.8-78.1]	72.1 [64.2-78.8]	69.9 [63.7-76.9]	0.1140
Male gender	245 (44.8)	139 (49.8)	106 (39.6)	0.016
Pneumonia on admission	143 (27.7)	47 (18.9)	96 (35.8)	<0.0001
Bronchiectasis	104 (26.4)	36 (18.4)	68 (34.3)	<0.0001
FEV_1 (litres)	0.71 [0.54-0.96]	0.66 [0.52-0.89]	0.77 [0.57-1.05]	0.0033
FEV_1 % predicted	34 [26-43]	32 [24-39]	35 [27-47]	0.0042
NIV ceiling of treatment	286 (52.3)	108 (38.7)	178 (66.4)	<0.0001
Pre-NIV pH	7.27 [7.21-7.3]	7.28 [7.23-7.31]	7.25 [7.2-7.29]	0.0002
Pre-NIV pCO2 (kPa)	9.91 [8.43-11.50]	9.36 [8.16-11]	10.34 [8.89-11.8]	0.0002
Pre-NIV pO2 (kPa)	7.83 [6.73-9.49]	9.06 [7.34-11.05]	7.22 [6.27-7.96]	0.0001
RF to NIV (hours)	1.83 [1-3.67]	1.63 [1-3.32]	2.08 [1.23-4.03]	0.0016
Duration of NIV (days)	5.07 [3.04-7.1]	5.07 [3.04-8.12]	4.06 [2.03-7.10]	0.006
Maximum IPAP (cmH_2O)	16 [14-20]	15 [12-18]	18 [15-21]	<0.0001
Maximum EPAP (cmH_2O)	5 [4-6]	5 [4-5]	5 [4-6]	<0.0001
Maximum oxygen (L/min)	5 [3-10]	8 [5-13]	4 [2-6]	<0.0001
Transferred to ITU	17 (3.1)	5 (1.8)	12 (4.5)	0.07
Intubated	10 (1.8)	5 (1.8)	5 (1.9)	0.953
In-hospital mortality	104 (19)	49 (17.6)	55 (20.5)	0.378
Time to in-hospital mortality (days)	9.13 [5.07-14.20]	9.13 [6.09-19.28]	9.13 [5.07-12.18]	0.5398
Length of stay (days)†	10.15 [6.09-17.25]	11.16 [7.10-19.28]	9.13 [6.09-13.19]	0.0001

Abbreviations: CT, computed tomography; FEV_1, forced expiratory volume in one second; NIV, non-invasive ventilation; RF to NIV, time from diagnosis of respiratory failure to application of NIV; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; ITU, intensive care unit. †Length of stay calculated for patients who survived to hospital discharge (n=443). Non-parametric data expressed as median [inter-quartile range] and analysed using the Wilcoxon rank-sum test. Categorical data expressed as number (percentage) and analysed using the Chi-squared test. A p-value <0.05 was considered statistically significant.

Figure Legends

Figure 1. Inpatient NIV referral pathway.

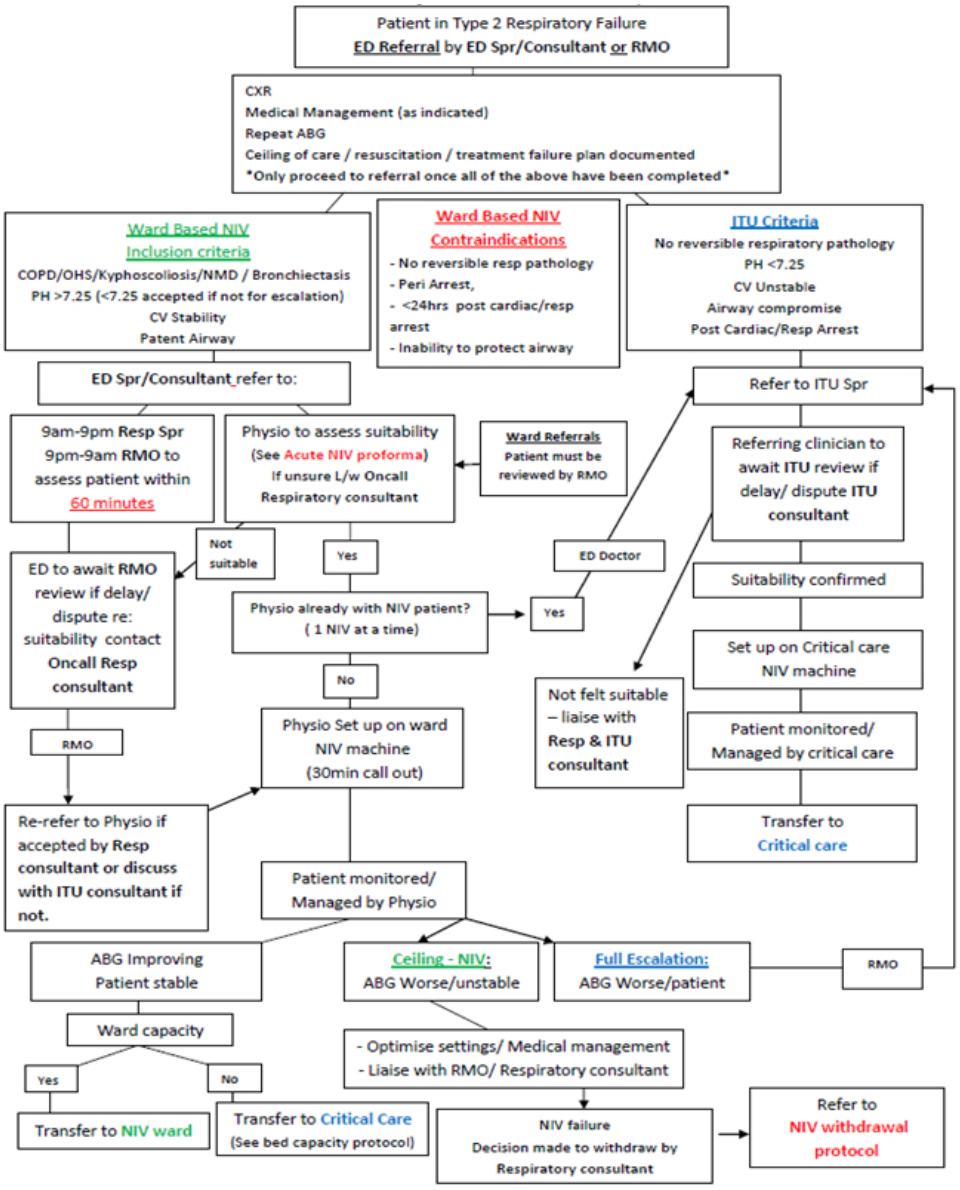

Figure 1. Inpatient NIV referral pathway.

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